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REVIEW ARTICLE

HEART versus GRACE Score in Predicting the Outcomes of Patients with Acute Coronary Syndrome; a Systematic Review and Meta-Analysis

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Abstract: **Introduction:** Several scoring systems have been proposed to predict the outcomes of patients with ischemic heart disease. Global Registry of Acute Coronary Events (GRACE) and History, ECG, Age, Risk Factors, and Troponin (HEART) scores are two of the more widely used risk prediction tools in patients with acute coronary syndrome (ACS). The present systematic review and meta-analysis aimed to compare the value of GRACE and HEART scores in the outcome prediction of ACS patient. **Methods:** The online databases of Medline, Embase, Web of Science, and Scopus were search until September 2022 for articles directly comparing GRACE and HEART scores value in prediction of outcome in patients with ACS. GRACE score cut-offs were categorized into two groups of less than and equal to 100 and more than 100, and HEART score cut-offs were categorized into three groups of less than 4, equal to 4, and more than 4. Investigated outcomes were major adverse cardiovascular events (MACE), acute myocardial infraction (AMI) and all-cause mortality. **Results:** 25 articles were included. The sensitivity and specificity of the GRACE score for prediction of MACE were 0.96 and 0.26 for cut-offs of ≤ 100, and 0.58 and 0.69 for cut-offs of >100, respectively. The sensitivity and specificity of the HEART score for prediction of MACE were 0.99 and 0.16 for cut-offs less than 4, 0.93 and 0.47 for equal to 4, and 0.77 and 0.78 for cut-offs greater than 4. GRACE score was shown to be predictive of AMI with sensitivity and specificity of 0.95 and 0.29, respectively. The analysis for the value of HEART score in the prediction of AMI a sensitivity and specificity of 0.94 and 0.48, respectively. The risk scores were not found to be suitable predictors of all-cause mortality. **Conclusion:** The results demonstrated the low specificity of GRACE and HEART scores in predicting the MACE, AMI and all-cause mortality, irrespective of the utilized cut-off. Considering the acceptable sensitivity of two scores in predicting the MACE and AMI, these scores were more suitable to be used as a rule-out tool for identification of ACS patients with low risk of developing adverse outcomes.

Keywords: Acute coronary syndrome; risk assessment; sensitivity; specificity; decision tools

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1. Introduction

Ischemic heart disease (IHD) is the most common cardiovascular disease and accounts for a vast amount of cardiovascular disease burden. It has been speculated that IHD was the cause of 9.14 million deaths in 2019 (1). Knowledge of the outcome of cardiovascular diseases can aid in the timely identification of high-risk patients and their management (2). Several scoring tools and markers have been proposed to predict the outcomes of cardiovascular diseases, especially mortality and major adverse cardiovascular events (MACE) (3-5). Global Registry of Acute Coronary Events (GRACE)

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and History, ECG, Age, Risk Factors, and Troponin (HEART) scores are two of the more widely used risk prediction tools in patients with acute coronary syndrome (ACS).

The GRACE score was introduced in 2007 and is calculated based on patient's age, killip class, heart rate, systolic blood pressure, ST segment changes, creatinine levels, and elevated cardiac markers to assess the risk of unfavorable outcomes in ACS patients (6). The HEART risk score was introduced in 2008 for identification of ACS patients with a higher risk of adverse outcomes (7). The predictive value of these tools has been investigated in ACS patients with promising results (2, 7-11).

In a recent systematic review and meta-analysis, Ke et al. (12) have indirectly evaluated GRACE and HEART scores in the prediction of MACE in ACS patients. Their results have demonstrated that HEART and GRACE scores could predict MACE with a sensitivity of 96% and 78% and specificity of 50% and 56%, respectively, and have concluded that HEART is more accurate than GRACE in the prediction of MACE in ACS patients.

Considering that direct comparisons are preferred as a basis for drawing conclusions, the present systematic review and meta-analysis was designed with the aim of directly comparing the value of GRACE and HEART scores in the prediction of ACS patient outcomes.

2. Methods

2.1. Study design and search strategy

This systematic review and meta-analysis was designed to evaluate and compare the value of HEART and GRACE tools in the prediction of ACS patient outcomes. P (patients): acute coronary syndrome patients, I (Index test): GRACE and HEART tools, C (Comparison):

ACS patients without the outcome of the study, O (Outcome): Major adverse cardiovascular events (MACE), Acute myocardial infarction (AMI), and all-cause mortality were chosen as the definition of PICO for the current review. MeSH terms of PubMed and Emtree terms of Embase databases were used to acquire related keywords. Chosen keywords were further tailored for the aim of this study by reviewing relevant articles and consultation with experts in the field. The online databases of PubMed, Embase, Web of Science, and Scopus were searched until September 10th, 2022, with the specific search strategies devised for each database (Supplementary material 1). A manual review of Google and Google scholar search engines and references of relevant articles was also performed to access any possibly missed studies.

2.2. Selection criteria

All articles with direct comparisons of GRACE and HEART scores in the adult population were included. The exclusion criteria of this study were review articles, non-English articles, articles with a design of indirect comparison, case series, duplicate records, and articles with no report of required data for this review.

2.3. Data extraction

The title and abstract of the retrieved records from online databases were screened by two independent reviewers and after the full-text screening, relevant studies were included. Reported data were extracted into a checklist designed according to PRISMA guidelines. The information in the checklist comprised study characteristics (first author, year, country), sample size, age, and male number, the outcome of the study and its definition, event rate of the whole population, and the number of patients who developed outcome in each group, follow-up duration, sensitivity, specificity, true and false positives, and true and false negatives. Any conflicts of opinion were resolved by consulting a third reviewer.

2.4. Quality assessment and Certainty of evidence

The quality of the included articles was evaluated using the Quality Assessment of Prognostic Accuracy Studies (QUAPAS) risk of bias assessment tool (13). According to this tool, studies are evaluated in two sections of risk of bias (consisting of patient selection, index test, reference standard, flow and timing and analysis) and applicability (consisting of patient selection, index test, and reference standard).

The certainty of evidence of the included articles was evaluated by the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) guidelines (14).

2.5. Statistical analysis

STATA 17.0 statistical software was used to perform the analysis. Reported data were recorded as true and false positives and true and false negatives. "midas" package was used to analyze the data. Findings were reported as pooled sensitivity, pooled specificity, area under the curve (AUC), positive and negative likelihood ratios, and diagnostic odds ratio. Since the results of the articles were reported by different cut-offs, we stratified the analysis based on the reported cut-offs. For this purpose, we categorized GRACE score cut-offs into two groups of less than and equal to 100 and more than 100, and HEART score cut-offs into three groups of less than 4, equal to 4, and more than 4. The publication bias of the included studies was assessed using Deeks' asymmetry funnel plot.

3. Results

3.1. Study flow and characteristics

The systematic search in online databases yielded 1860 non-duplicate records. 59 reports were assessed for eligibility after the title and abstract screening and 25 articles were chosen to be included in this study (2, 15-38). 3 articles were retrieved by manual search, none of which were included (Figure 1).
The articles comprised data on 21389 suspected ACS patients (55.01% male), with a follow-up of at least 30 days (15 articles) with a maximum follow-up time of roughly 8 years. The assessed outcomes were MACE (18 articles), AMI (6 articles), and all-cause of mortality (3 articles). 19 studies were designed as prospective cohorts, and 6 were retrospective cohorts. The characteristics of the included articles are demonstrated in table 1.

3.2. Value of GRACE and HEART risk scores in the prediction of MACE

Studies included 17697 patients (56.1% male) with an event rate of 18.54% (3282 patients) in the evaluation of the value of GRACE and HEART scores in the prediction of MACE.
The results of the analysis for GRACE score with cut-offs of less than and equal to 100 and more than 100 showed AUCs of 0.71 (95% CI: 0.67, 0.75) and 0.66 (95% CI: 0.62, 0.70), respectively. The sensitivity and specificity of the GRACE score were 0.96 (95% CI: 0.90, 0.98) and 0.26 (95% CI: 0.16, 0.40) for cut-offs of ≤ 100 and 0.58 (95% CI: 0.53, 0.64) and 0.69 (0.61, 0.77) for cut-offs of >100, respectively.
The AUC of HEART scores less than 4 and equal to 4 was calculated as 0.98 (95% CI: 0.96, 0.99) and 0.72 (95% CI: 0.68, 0.76), respectively. The AUC of HEART scores more than 4 was 0.84 (95% CI: 0.81, 0.87). The sensitivity and specificity of the HEART scores were 0.99 and 0.16 for scores less than 4, 0.93 and 0.47 for equal to 4, and 0.77 and 0.78 for scores greater than 4. Based on the presented data, the HEART score is best predictive of MACE with a cut-off score of 4 (Table 2). Although it should be mentioned that only 3 articles had data on the prognostic value of HEART score with cut-offs of less than 4 (Figure 2 and Table 2).

3.3. Value of GRACE and HEART risk scores in the prediction of AMI

Studies comprised 3591 patients (55.4% male) with an event rate of 13.23% (475 patients) in the assessment of the prognostic values of GRACE and HEART for the prediction of AMI. AUC of the GRACE score for the prediction of AMI was 0.72 (95% CI: 0.68, 0.76) and the sensitivity and specificity were 0.95 (95% CI: 0.86, 0.98) and 0.29 (95% CI: 0.16, 0.46), respectively (Figure 3 and Table 2). All studies, except two (21, 23), utilized cut-offs of less than 100. A sensitivity analysis was performed for reports with cut-offs of less than 100 and the results demonstrated an AUC of 0.76 (95% CI: 0.72, 0.80), sensitivity of 0.98 (95% CI: 0.93, 0.99) and specificity of 0.18 (95% CI: 0.09, 0.31) for the value of GRACE score in prediction of AMI.
The analysis for the value of HEART score in the prediction of AMI revealed an AUC of 0.86 (95% CI: 0.82, 0.88) and a sensitivity and specificity of 0.94 (95% CI: 0.88 and 0.97) and 0.48 (95% CI: 0.32, 0.64), respectively. One article had utilized a cut-off of 3 (16), two articles had not reported the utilized cut-off (21, 24) and the remaining three articles had utilized a cut-off of 4. A sensitivity analysis was performed for the three articles utilizing a cut-off of 4 and the results showed an AUC of 0.83 (95% CI: 0.80, 0.86), a sensitivity of 0.94 (95% CI: 0.86, 0.97) and a specificity of 0.51 (95% CI: 0.36, 0.66).

3.4. Value of GRACE and HEART risk scores in the prediction of all-cause mortality

1903 patients (79.8% male, 15.24% event rate) were included in the meta-analysis for the value of GRACE and HEART scores in the prediction of all-cause mortality. The results of the analysis showed an AUC of 0.75 (95% CI: 0.71, 0.79) for GRACE and 0.65 (95% CI: 0.61, 0.69) for the HEART score. The sensitivity and specificity of GRACE were 0.82 (95% CI: 0.75, 0.87) and 0.51 (95% CI: 0.42, 0.61), respectively and the sensitivity and specificity of HEART score were 0.78 (95% CI: 0.57, 0.90) and 0.56 (95% CI: 0.49, 0.62). Two studies utilized a cut-off of more than 100 for the GRACE score and one study utilized a cut-off of 4 for the HEART score, the remaining studies had not reported the cut-off used. Due to the scarce number of included studies, sensitivity analysis was not performed (Figure 4, Table 2).

3.5. Publication bias

Publication bias was only assessed for the outcome of MACE, which had more than 10 included studies. No publication bias was observed in the evaluation of the value of GRACE and HEART scores in the prediction of MACE (Figure 5).

3.6. Risk of bias assessment

The risk of bias in the domain of patient selection was evaluated to be unclear in eight studies, due to no mention of their sampling method, and high in three studies due to convenient sampling. Eight studies had not mentioned the criteria for choosing the risk scores cut-offs and were rated as unclear in risk of bias in the domain of index test and four studies were rated as high in risk of bias in this domain due to choosing their cut-offs based on the calculated AUCs. Outcome assessment protocol was unclear in seven articles and one article did not provide any outcome definition and was rated as high in risk of bias in the domain of outcome. Three studies were rated as unclear in risk of bias in the domain of flow and timing due to possible loss to follow-ups. Two stud-

ies were rated as unclear in the risk of bias in the domain of analysis due to having possible competing events. One study was rated as high in the applicability of outcome due to no outcome definition. The articles were rated as low in the remainder of the domains. Overall, the included studies were judged to have a serious risk of bias (Table 3).

3.7. Certainty of evidence

The certainty of the evidence of the included studies was assessed using GRADE guidelines. The included studies were designed as cohort studies and according to GRADE guidelines, the base level of evidence was set as high for comparative test accuracy studies.

The level of evidence for the outcome of MACE was rated down one score due to the serious risk of bias in included articles and thus both scores had a moderate level of evidence for the outcome of MACE. The level of evidence in the outcomes of AMI and all-cause mortality was rated down two scores for serious risk of bias, and the inability of assessing publication bias due to the limited included studies. The level of evidence for outcomes of AMI and all-cause mortality was rated as low for both risk scores (Table 4).

4. Discussion

The current study is the first meta-analysis conducted on the direct comparison of the value of GRACE and HEART scores for the prediction of adverse outcomes in ACS patients. We evaluated the predictive value of GRACE and HEART scores in outcomes of MACE, AMI, and all-cause mortality and our results showed that utilizing GRACE and HEART scores with appropriate cut-offs can predict MACE and AMI with acceptable sensitivities.

The included studies had utilized various cut-off values. Our analysis demonstrated that the predictive performance of the GRACE score for the outcome of MACE greatly improves when utilized with cut-off values less than 100 (Sensitivity of 0.96 for cut-off values less than 100 and sensitivity of 0.59 for cut-off values more than 100). The predictive value of the HEART score was shown to be higher when utilized with cut-offs of less than 4 (Sensitivity of 0.99), or equal to 4 (sensitivity of 0.93), and our results suggest that utilization of HEART score with a cut-off value of more than 4 (sensitivity of 0.77) cannot be administered as a predictive tool for MACE.

GRACE and HEART tools were also demonstrated to be good predictors of AMI, with sensitivities of 0.95 and 0.94 respectively. Further analysis revealed that utilization of the GRACE score with cut-off values of less than 100, slightly improves its predictive value for AMI (sensitivity of 0.98) while subgrouping the analysis of the HEART score by the cut-off value of 4, did not reveal any significant changes to its predictive value for AMI.

In contrast to the acceptable performance of GRACE and HEART scores for the prediction of MACE and AMI, in our analysis, these scores were not found to be proper predictors of all-cause mortality (sensitivities of 0.82 and 0.78 respectively). Although it should be mentioned that our results are limited by the scarce number of included studies investigating the outcome of all-cause mortality. Overall, our results have demonstrated low specificity for GRACE and HEART scores in all three outcomes, irrespective of the utilized cut-off. We believe this reiterates the fact that such scores are more suitable to be used as a rule-out tool for identification of ACS patients with low risk of developing adverse outcomes, rather than as a rule-in tool to identify patients with higher chances of developing adverse outcomes.

Previous systematic reviews have evaluated the predictive value of GRACE and HEART scores separately or as an indirect comparison. Van Den Berg et al, suggested that the HEART score could be predictive of MACE with a sensitivity and specificity of 0.96 and 0.47 respectively (39). Whereas Ke et al (12) indirectly compared the predictive performance of GRACE and HEART scores and demonstrated a sensitivity and specificity of 0.96 and 0.50 for GRACE and sensitivity and specificity of 0.78 and 0.56 for HEART scores in the prediction of MACE. Our results for the predictive performance of GRACE for MACE are in line with previous reviews, however, our results demonstrated a better predictive value for the HEART score. Moreover, we suggest that GRACE and HEART scores can also be used to predict AMI in ACS patients. Although the specified cut-off value chosen for the interpretation of these risk scores is important and can vastly affect their predictive capabilities.

Considering the fairly similar predictive performances of GRACE and HEART scores in our review, the differences in their design should be kept in mind for better application of these scores. HEART score variables are more readily available, and the overall score can be easily calculated. This score relies on the judgment of patient history suspicion which can be challenging due to no exact definition for high, moderate, or slight suspicion, however it has been argued that incorporating clinical gestalt can improve the performance capabilities of the score (26). GRACE score has been found to be more complex which might require a computer for calculations. There are also fundamental differences in the aims of each score. While HEART score aims to identify low-risk chest pain patients for early discharge, GRACE score was derived for high-risk patients investigating the need for invasive therapy and not for evaluating individuals with undifferentiated chest pain (40-42). It should also be noted that GRACE and HEART scores should be used to enhance the decision-making process of the physician and they are never meant to replace clinical decision-making.

5. Limitations

This systematic review has a few limitations. First, the included studies had differing patient selection criteria. While some studies had included all suspected ACS patients, some had only investigated non-ST elevation myocardial infarction (MI) ACS patients, and few studies had only included ST elevation MI ACS patients. Thus, although our analysis is indicative of all types of ACS patients, further studies could evaluate the value of GRACE and HEART scores in specific ACS patient settings. The definition of MACE in the included articles could affect the predictive value of the GRACE and HEART scores. The articles had varying MACE definitions, ranging from a combined endpoint of death or MI to more composite endpoints, which made a subgroup analysis impossible. The included articles had not reported the treatment plan of their patients. Considering that different treatment regimens can have an effect on the outcome of patients, future studies could aim to evaluate the predictive value of scoring systems in populations receiving uniform treatments.

6. Conclusion

The results demonstrated the low specificity of GRACE and HEART scores in predicting the MACE, AMI and all-cause mortality, irrespective of the utilized cut-off. Considering the acceptable sensitivity of two scores in predicting the MACE and AMI, these scores were more suitable to be used as a rule-out tool for identification of ACS patients with low risk of developing adverse outcomes.

7. Declarations

7.1. Acknowledgments

None.

7.2. Conflict of interest

The authors declare that they have no competing interests.

7.3. Funding and support

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7.4. Authors' contribution

Study design: MY, RM
Data gathering: AK, PG, SAF
Analysis: MY, KA
Interpretation of results: all authors
Drafting and revising: all authors
All authors read and approved final version.

7.5. Using artificial intelligence chatbots

None.

7.6. Availability of data and materials

The gathered data and checklist can be provided to qualified researchers with the intent of replicating the procedure and results.

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Table 1: Characteristics of included studies

Study	Country	Design	Follow up (day)	Sample size	Male (n)	Age* (year)	Outcome: number	GRACE cut-off	HEART cut-off
Al-Zaiti 2018	US	RCS	30	750	433	59±17	MACE: 33	109	4
Carlton 2015	UK	PCS	30	959	564	58±13.3	AMI: 79	60, 80	3, 4
Chae 2016	South Korea	PCS	30	1024	594	58 (50-69)	MACE: 126	108	4
Chen 2016	China	PCS	30, 180	833	461	65.1±14.5	MACE: 121	109, 114	4, 5
Chew 2018	UK	PCS	42, 365	1642	858	59.35±18.54	MACE: 279 AMI: 180	76	4
Dinesh 2022	India	PCS	42	199	138	51.61±16.47	MACE: 76	119	7
Dupuy 2021	France	PCS	30	160	94	73 to 80	AMI: 37 Death: 13	NR	NR
Han 2017	Taiwan	RCS	180	249	203	61.7±14.91	Death: 41	121	NR
Hrecko 2022	Finland	RCS	30	250	126	78.5±8.2	AMI: 48	109	4
Huang 2021	China	PCS	30	509	293	59.77±14.9	MACE: 92	106	4
Juknevičienė 2022	Lithuania	PCS	180	146	95	63±13.4	AMI: 51	NR	NR
Liu 2017	Singapore	PCS	NR	797	542	NR	MACE: 146	108	5
Mingwei NG 2020	Singapore	PCS	30	1195	817	NR	MACE: 135	109	4
Poldervaart 2017	Netherlands	PCS	42	1748	937	62±14	MACE: 326	73	4
Reaney 2017	UK	PCS	30	1000	574	62.4±15.6	MACE: 189	56, 119	4, 7
Ruangsomboon 2020	Thailand	PCS	30	350	185	66.3±15.1	MACE: 59	56, 66	3, 4
Sakamoto 2016	Singapore	PCS	30	604	417	60.8±13.2	MACE: 215	76, 111	4, 5
Shin 2020	Korea	RCS	30, 90	1247	758	62±12.7	MACE: 211	109	4
Singer 2017	US	PCS	30	434	251	56.64±11.15	AMI: 80	51	4
Steiro 2021	Norway	RCS	30, 180	932	562	63±16.33	MACE: 191	90, 109	4
Tekin 2021	Turkey	PCS	30	381	195	NR	MACE: 105	115	6
Torralba 2020	Colombia	PCS	30	519	291	64.31±12.11	MACE: 224	109	4
Wong 2017	Hong Kong	PCS	30	1081	565	48±27	MACE: 164	50,75,100	1, 2
Yang 2022	China	RCS	2956	1494	1221	63 (53-72)	Death: 236	126	4
Zheng 2020	China	PCS	30	2886	1447	64±13.5	MACE: 590	81	4

Data are presented as mean ± standard deviation or median (interquartile range). AMI: Acute myocardial infarction, MACE: Major adverse cardiovascular event, NR: Not reported, PCS: Prospective cohort study, RCS: Retrospective cohort study

Table 2: Performance of GRACE and MACE scores in prediction of outcomes

System	cut-off	Sensitivity	Specificity	AUC	PLR	NLR	OR
Major adverse cardiovascular event (MACE)							
GRACE	≤100	0.96 (0.90, 0.98)	0.26 (0.16, 0.40)	0.71 (0.67, 0.75)	1.3 (1.1, 1.5)	0.17 (0.10, 0.27)	8 (5, 12)
	>100	0.58 (0.53, 0.64)	0.69 (0.61, 0.77)	0.66 (0.62, 0.70)	1.9 (1.5, 2.3)	0.60 (0.54, 0.67)	3 (2, 4)
HEART	<4	0.99 (0.97, 0.99)	0.16 (0.08, 0.29)	0.98 (0.96, 0.99)	1.2 (1.0, 1.3)	0.09 (0.03, 0.25)	13 (4, 36)
	4	0.93 (0.88, 0.96)	0.47 (0.40, 0.54)	0.72 (0.68, 0.76)	1.8 (1.6, 2.0)	0.14 (0.08, 0.23)	13 (8, 21)
	>4	0.77 (0.63, 0.87)	0.78 (0.59, 0.90)	0.84 (0.81, 0.87)	3.6 (1.8, 7.2)	0.29 (0.17, 0.49)	12 (5, 34)
Acute myocardial infarction (AMI)							
GRACE	NA	0.95 (0.86, 0.98)	0.29 (0.16, 0.46)	0.72 (0.68, 0.76)	1.3 (1.1, 1.6)	0.18 (0.10, 0.33)	7 (4, 12)
HEART	NA	0.94 (0.88, 0.97)	0.48 (0.32, 0.64)	0.86 (0.82, 0.88)	1.8 (1.4, 2.4)	0.12 (0.08, 0.21)	14 (9, 23)
All-cause mortality							
GRACE	NA	0.82 (0.75, 0.87)	0.51 (0.42, 0.61)	0.75 (0.71, 0.79)	1.7 (1.5, 1.9)	0.36 (0.29, 0.44)	5 (4, 6)
HEART	NA	0.78 (0.57, 0.90)	0.56 (0.49, 0.62)	0.65 (0.61, 0.69)	1.8 (1.3, 2.4)	0.39 (0.18, 0.89)	4 (1, 13)

All measures are presented with 95% confidence interval. PLR: Positive likelihood ratio; NLR: Negative likelihood ratio; OR: Diagnostic odds ratio; AUC: Area under the curve; 95% CI: Confidence interval; NA: Not applicable.

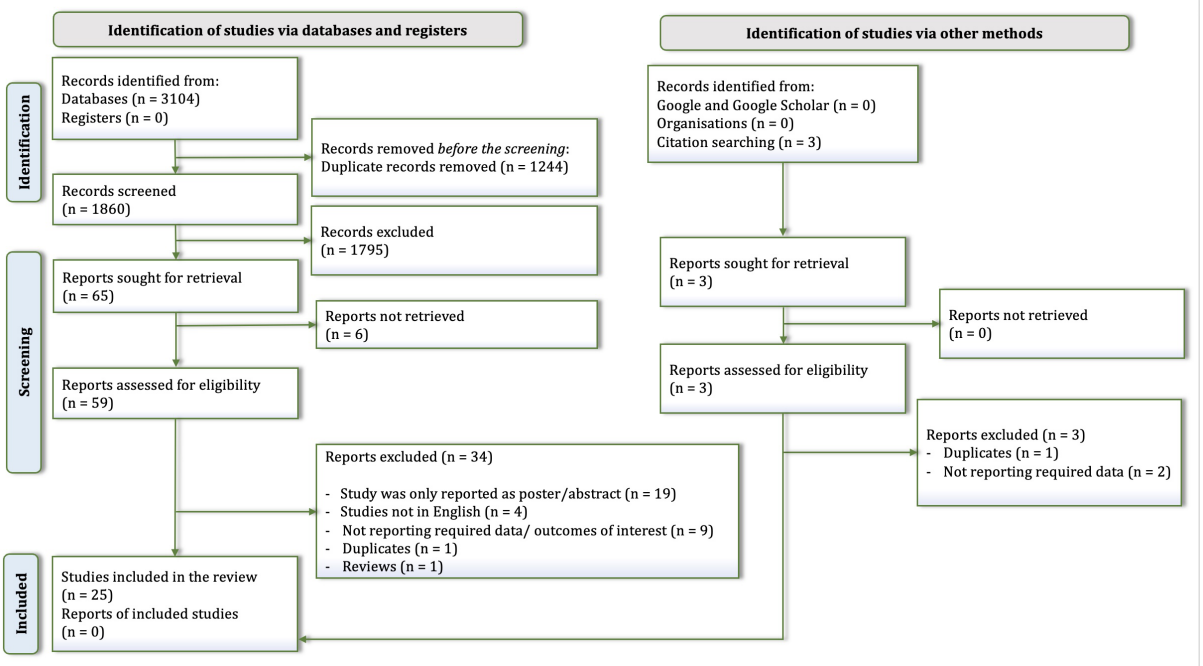

Figure 1: PRISMA flow diagram.

Table 3: Risk of bias assessment

Study, year	Risk of Bias					Applicability				Overall
	Patient selection	Index test	Outcome	Flow and timing	Analysis	Patient selection	Index test	Outcome	Flow and timing	
Al-Zaiti, 2018	Low	Low	Low	Unclear	Unclear	Low	Low	Low	Low	Some concern
Carlton, 2015	Low	Low	Low	Low	Unclear	Low	Low	Low	Low	Some concern
Chae, 2016	Unclear	Low	Low	Low	Low	Low	Low	Low	Low	Some concern
Chen, 2016	Low	Low	Unclear	Low	Low	Low	Low	Low	Low	Some concern
Chew, 2018	Low	Unclear	Unclear	Low	Low	Low	Low	Low	Low	Some concern
Dinesh, 2022	Low	Unclear	Unclear	Low	Low	Low	Low	Low	Low	Some concern
Dupuy, 2021	Unclear	Unclear	Low	Low	Low	Low	Low	Low	Low	Some concern
Han, 2017	Low	High	Low	Low	Low	Low	Low	Low	Low	Some concern
Hrecko, 2022	Low	Low	Unclear	Unclear	Unclear	Low	Low	Low	Low	Some concern
Huang, 2021	Unclear	Unclear	Low	Low	Low	Low	Low	Low	Low	Some concern
Jukneviciene, 2022	Low	Unclear	Low	Unclear	Unclear	Low	Low	Low	Low	Some concern
Liu, 2017	High	High	Low	Low	Low	Low	Low	Low	Low	Some concern
Mingwei, 2020	High	Low	Low	Low	Low	Low	Low	Low	Low	Some concern
Poldervaar, 2016	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Reaney, 2017	High	Low	Unclear	Low	Low	Low	Low	Low	Low	Some concern
Ruansomboon, 2020	Low	Unclear	Low	Low	Low	Low	Low	Low	Low	Some concern
Sakamoto, 2016	Unclear	Low	Unclear	Low	Low	Low	Low	Low	Low	Some concern
Shin, 2020	Low	Low	Unclear	Low	Low	Low	Low	Low	Low	Some concern
Singer, 2017	Unclear	Unclear	Low	Low	Unclear	Low	Low	Low	Low	Some concern
Steiro, 2021	Unclear	Low	Low	Low	Low	Low	Low	Low	Low	Some concern
Tekin, 2021	Unclear	High	High	Low	Low	Low	Low	High	Low	Some concern
Torralba, 2020	Unclear	Low	Low	Low	Low	Low	Low	Low	Low	Some concern
Wong, 2017	Low	Unclear	Low	Low	Low	Low	Low	Low	Low	Some concern
Yang, 2022	Low	High	Low	Low	Low	Low	Low	Low	Low	Some concern
Zheng, 2020	Low	Low	Low	Low	Low	Low	Low	Low	Low	Some concern

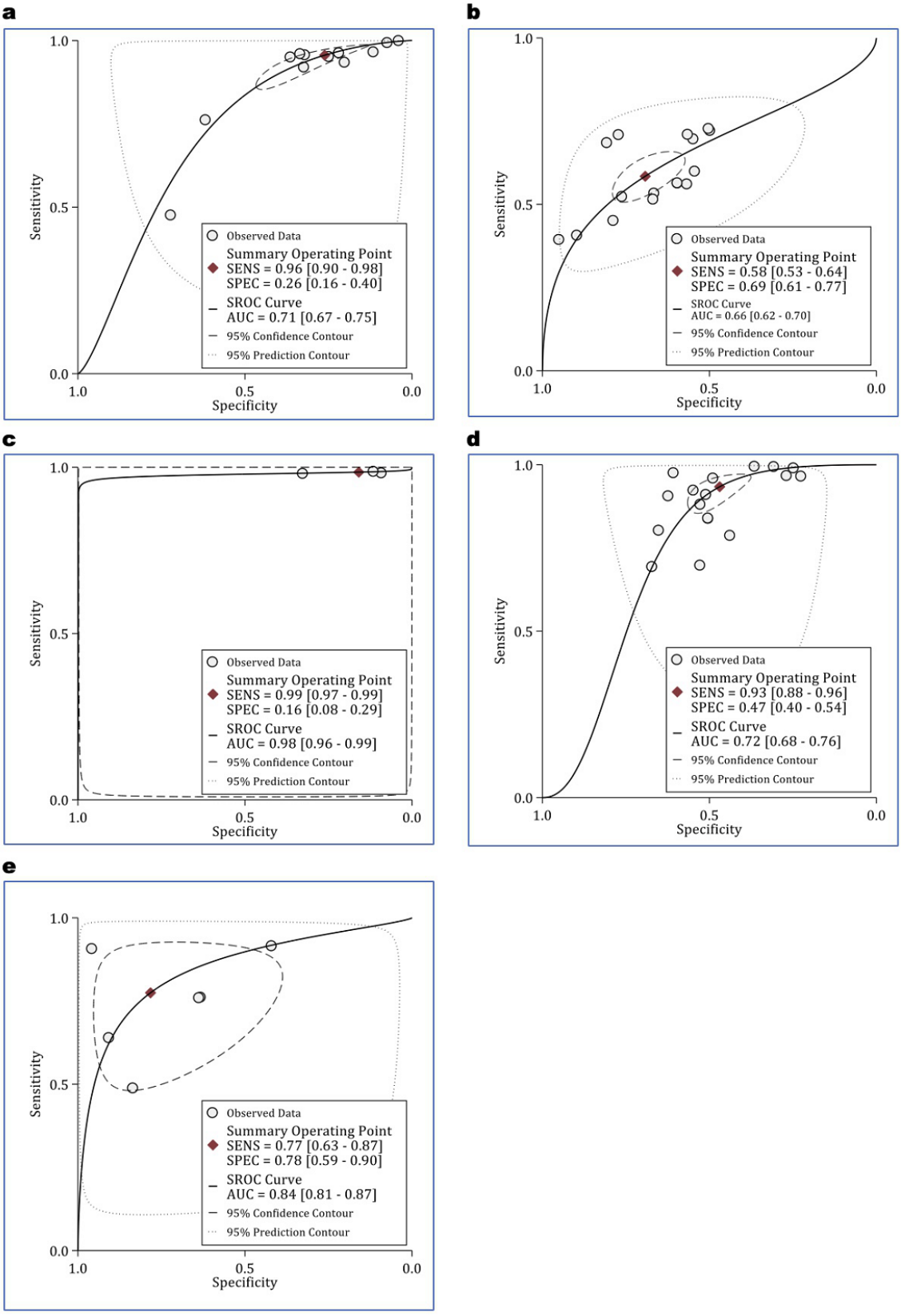

Figure 2: Performance of GRACE score with cut-off values of ≤ 100 (a) and > 100 (b) and HEART score with cut-off values < 4 (c), equal to 4 (d) and greater than 4 (e) in the prediction of major adverse cardiovascular events.

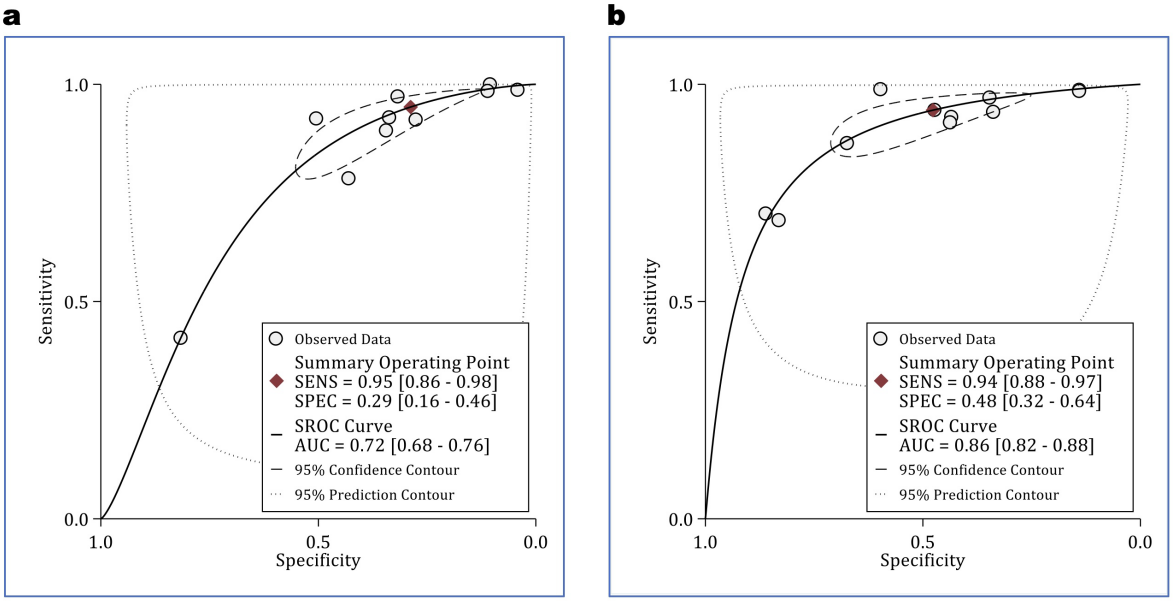

Figure 3: Performance of GRACE score (a) and HEART score (b) in the prediction of acute myocardial infarction.

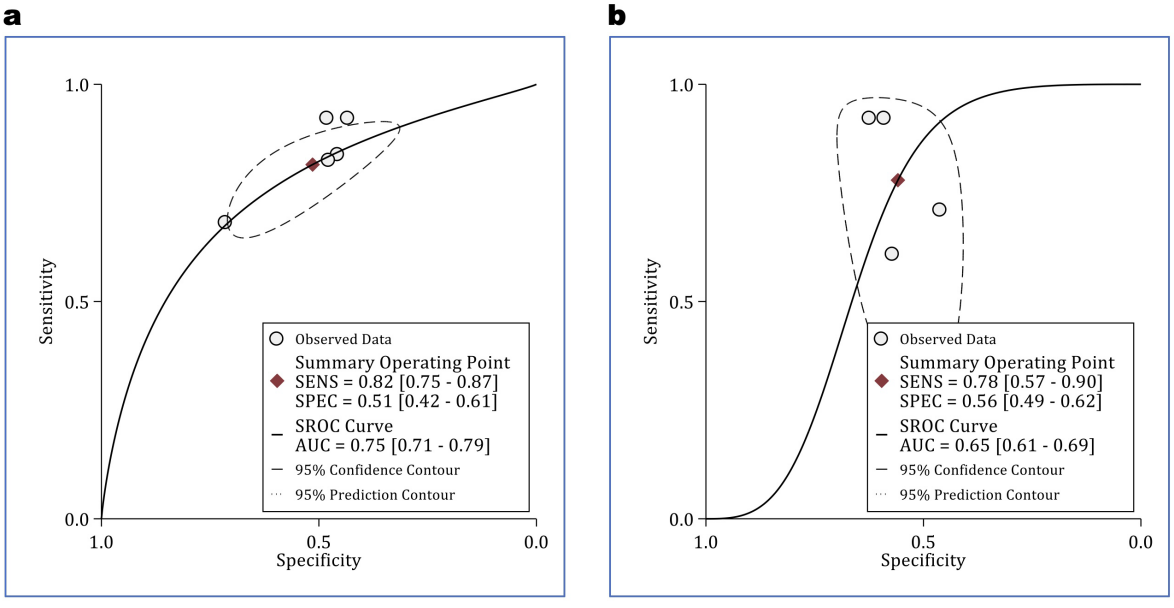

Figure 4: Performance of GRACE score (a) and HEART score (b) in the prediction of all-cause mortality.

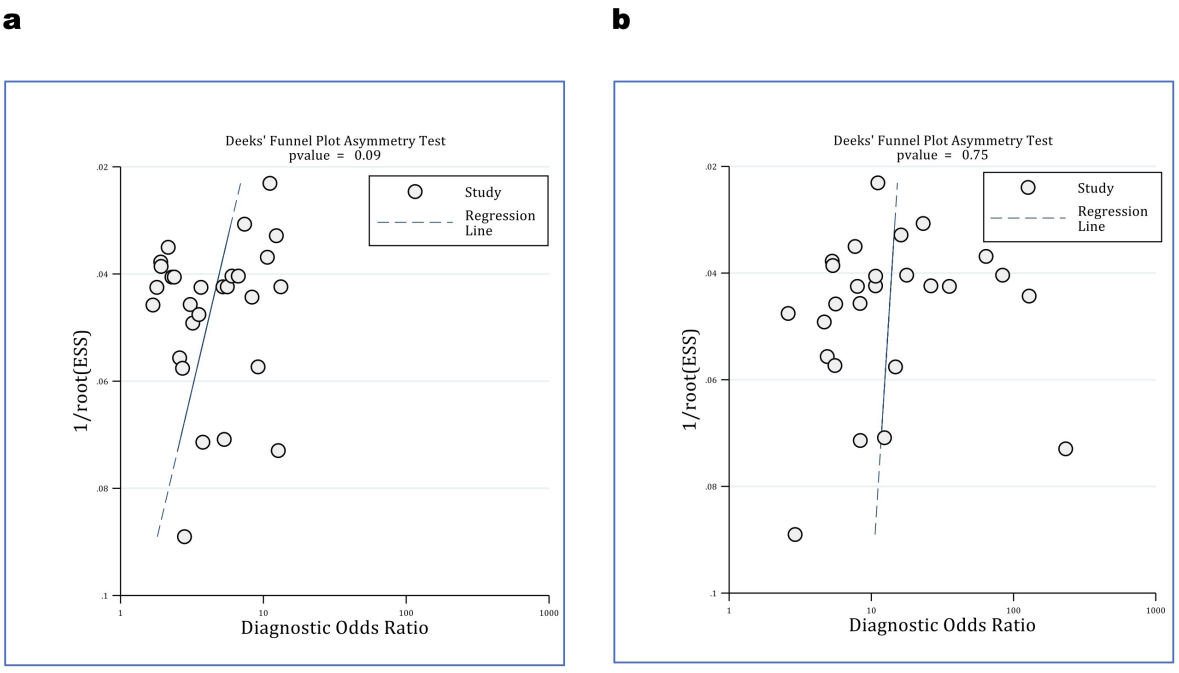

Figure 5: Publication bias of the included articles for the value of GRACE (a) and HEART (b) in the prediction of major adverse cardiovascular events.

Table 4: Certainty of evidence

Outcome		Study/ population	Study design	Factors that may decrease certainty of evidence					Certainty of evidence
				Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	
Major adverse cardiovascular event									
GRACE	Cut-offs ≤ 100	8 studies N = 10243	Cohort studies	Serious	Not serious	Not serious	Not serious	Not serious	◯⊕⊕⊕⊕ Moderate
	Cut-offs > 100	13 studies N = 10793							
HEART	Cut-off < 4	2 studies N = 1431	Cohort studies	Serious	Not serious	Not serious	Not serious	Not serious	◯⊕⊕⊕⊕ Moderate
	Cut-off = 4	14 studies N = 15239							
	Cut-offs > 4	6 studies N = 3814							
Acute myocardial infarction									
GRACE	Cut-offs: NA	6 studies N = 3591	Cohort studies	Serious	Not serious	Not serious	Not serious	Not applicable	◯⊕⊕⊕◯ Low
HEART	Cut-off: NA	6 studies N = 3591	Cohort studies	Serious	Not serious	Not serious	Not serious	Not applicable	◯⊕⊕⊕◯ Low
All-cause mortality									
GRACE	Cut-off: NA	3 studies N = 1903	Cohort studies	Serious	Not serious	Not serious	Not serious	Not applicable	◯⊕⊕⊕◯ Low
HEART	Cut-off: NA	3 studies N = 1903	Cohort studies	Serious	Not serious	Not serious	Not serious	Not applicable	◯⊕⊕⊕◯ Low

Supplementary Table 1: Search strategy

PubMed: ((Global registry acute coronary events[tiab] OR GRACE[tiab]) AND (HEART[tiab])) AND (SCOR*[tiab] OR Scal*[tiab] OR tool*[tiab] OR mode*[tiab] OR pathway[tiab]OR assessment*[tiab])
Embase: ('global registry of acute coronary events'/exp OR 'global registry of acute coronary events':ab,ti OR 'grace':ab,ti OR 'global registry for acute coronary events':ab,ti) AND ('scor*':ab,ti OR 'scal*':ab,ti OR 'tool*':ab,ti OR 'mode*':ab,ti OR 'pathway':ab,ti OR 'assessment*':ab,ti) AND ('history electrocardiogram age risk factors and troponin score'/exp OR 'history electrocardiogram age risk factors and troponin score' OR 'heart':ab,ti)
Scopus: TITLE-ABS-KEY("global registry of acute coronary events" OR "grace" OR "global registry for acute coronary events") AND TITLE-ABS-KEY("scor*" OR "scal*" OR "tool*" OR "mode*" OR "pathway" OR "assessment*") AND TITLE-ABS-KEY("history electrocardiogram age risk factors and troponin score" OR "heart")
Web of Science (((TS=("global registry of acute coronary events" OR "grace" OR "global registry for acute coronary events"))) AND TS=("scor*" OR "scal*" OR "tool*" OR "mode*" OR "pathway" OR "assessment*")) AND TS=("history electrocardiogram age risk factors and troponin score" OR "heart")